Review Article

The Peritoneal Paradox: Deciphering the Conflicting Evidence for HIPEC in Primary versus Recurrent Ovarian Cancer

Abstract

Advanced-stage ovarian cancer is characterized by high mortality and frequent peritoneal recurrence. "Hyperthermic Intraperitoneal Chemotherapy" (HIPEC), which delivers heated chemotherapeutic agents directly into the peritoneal cavity following cytoreductive surgery (CRS), aims to enhance local cytotoxicity against microscopic residual disease. A comprehensive Boolean search was conducted using PubMed/Medline, Google Scholar, Embase and Scopus to identify relevant studies on the use of HIPEC for primary and recurrent ovarian cancer. Evidence from randomized controlled trials (RCTs) indicates that HIPEC significantly improves overall survival (OS) in primary advanced-stage disease, specifically when administered during interval debulking surgery (IDS) following neoadjuvant chemotherapy (NACT). Conversely, its role in primary debulking and recurrent settings remains controversial. While some trials show benefits, others, including the HORSE trial, found no significant difference in OS. Furthermore, HIPEC is associated with increased morbidity, including longer operative times and a higher incidence of grade 3-5 adverse events. Consequently, current guidelines primarily recommend HIPEC as an option for stage III patients during IDS. While a promising advance, further research is required to standardize protocols and optimize patient selection.

Keywords: Hyperthermic Intraperitoneal Chemotherapy; Ovarian cancer; Cytoreductive surgery; Interval debulking surgery; Overall survival; Secondary cytoreductive surgery; Progression-free survival; Neoadjuvant chemotherapy

1. Introduction

Ovarian cancer remains the most lethal gynecological malignancy worldwide, with a five-year relative survival rate of less than 50% [1-3]. The poor prognosis is primarily attributed to the fact that over two-thirds of patients present with advanced-stage disease (FIGO stages III and IV) at diagnosis, characterized by extensive intraperitoneal dissemination [4,5]. This hallmark spread is strongly associated with treatment failure and high recurrence rates, as the peritoneal cavity often harbors microscopic residual disease even after seemingly successful surgery [6]. The current standard of care for advanced-stage disease typically involves primary debulking surgery (PDS) followed by platinum-based intravenous chemotherapy, or neoadjuvant chemotherapy (NACT) followed by interval debulking surgery (IDS) for those whom initial surgery is not feasible [7-9]. Despite these efforts, recurrence occurs in approximately 80% of patients, mostly within the peritoneum [5,10]. "Hyperthermic Intraperitoneal Chemotherapy" (HIPEC) has emerged as an innovative therapeutic strategy to address this. By delivering

heated chemotherapeutic agents directly into the peritoneal cavity immediately following cytoreduction, HIPEC aims to enhance local cytotoxicity and target microscopic residual tumors that systemic therapy may not reach effectively [11-13].

2. Methodology

A Boolean search was conducted in PubMed/Medline, Google Scholar, Embase and Scopus databases using the keywords "Hyperthermic Intraperitoneal Chemotherapy", "Ovarian cancer", "Cytoreductive surgery", "Interval debulking surgery", and "Secondary cytoreductive surgery". Two independent authors assessed and extracted the data. All English language articles, including original full-length articles, meta-analyses, review articles and case reports were included. Preprints and any articles without details on application of HIPEC in ovarian cancer were excluded. There was no restriction based on the year (how many years were included, was it 5 years or 10 years?). All studies (how many studies in total were reviewed?) were reviewed, and findings were summarised.

3. Technique

HIPEC is performed as an adjuvant procedure during the same surgical session as cytoreduction, once the surgeon has achieved minimal residual disease [14]. There are two primary surgical techniques utilized. In open technique (Coliseum technique), a plastic cuff is usually stitched to the abdominal wall edges to raise them, creating a well. The abdomen is filled with saline, and input/output drains are attached to an external pump and heat exchanger. Perfusion begins once the target temperature is reached, and the surgeon may manually manipulate the fluid to ensure even distribution [11,15].

The abdominal wall is temporarily or definitively closed after catheter placement in the closed technique. This allows for increased intra-abdominal pressure, which may theoretically enhance drug penetration, and minimizes the risk of chemotherapy aerosolization for the theatre staff. In both methods, catheters (typically two for inflow and two for outflow) are strategically positioned to ensure the heated solution circulates throughout all peritoneal surfaces [16,17].

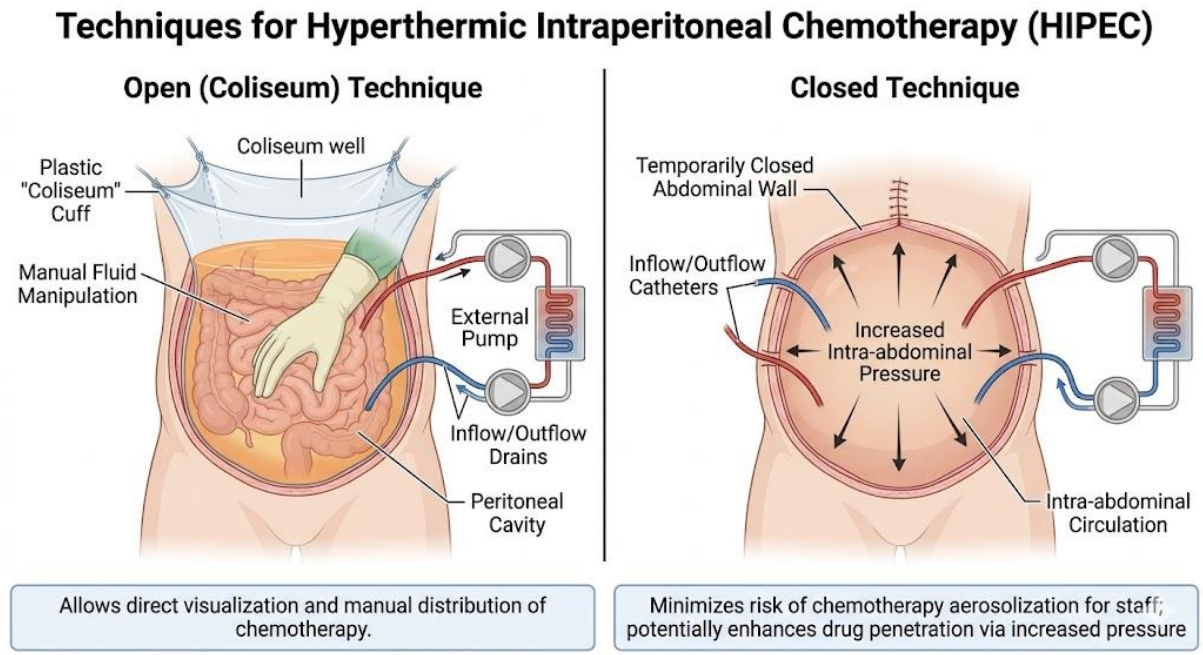

Figure 1. Techniques for HIPEC

4. Administration

The administration of HIPEC requires specialized equipment, including a HIPEC machine with a heat exchanger and pumps, and a trained multidisciplinary team including a perfusionist [18]. Cisplatin is the most commonly used and recommended agent, often at doses of 75-100 mg/m2 body surface area (BSA). Other agents evaluated in trials include Carboplatin (800 mg/m2 BSA), Paclitaxel (60–175 mg/m2 BSA), and occasionally Doxorubicin or Mitomycin C [19,20]. The solution is heated to a target range of 40°C to 43.3°C (104°F to 110°F). Perfusion typically lasts for 60 to 90 minutes. Chemotherapy is usually diluted in 2–3 liters of saline or specialized carrier solutions to facilitate circulation [14,21].

5. Mode of Action

HIPEC leverages the synergistic effects of hyperthermia and high-dose local chemotherapy. Hyperthermia increases the penetration depth of chemotherapy into the peritoneal surfaces, overcoming the plasma-peritoneal barrier [14,15]. Heat is directly toxic to tumor cells, disrupting cell membrane permeability and inhibiting angiogenesis [22,23]. Mild hyperthermia is known to degrade the *BRCA* protein, leading to a transient impairment of homologous recombination [24]. This restricts the ability of cancer cells to repair double-strand DNA breaks caused by platinum agents.

Heat shock protein activation triggers a systemic immune response, potentially targeting metastatic cells outside the local area [25]. Delivering drugs directly to the peritoneum achieves concentrations significantly higher than those possible with intravenous administration, while limiting systemic side effects [26,27].

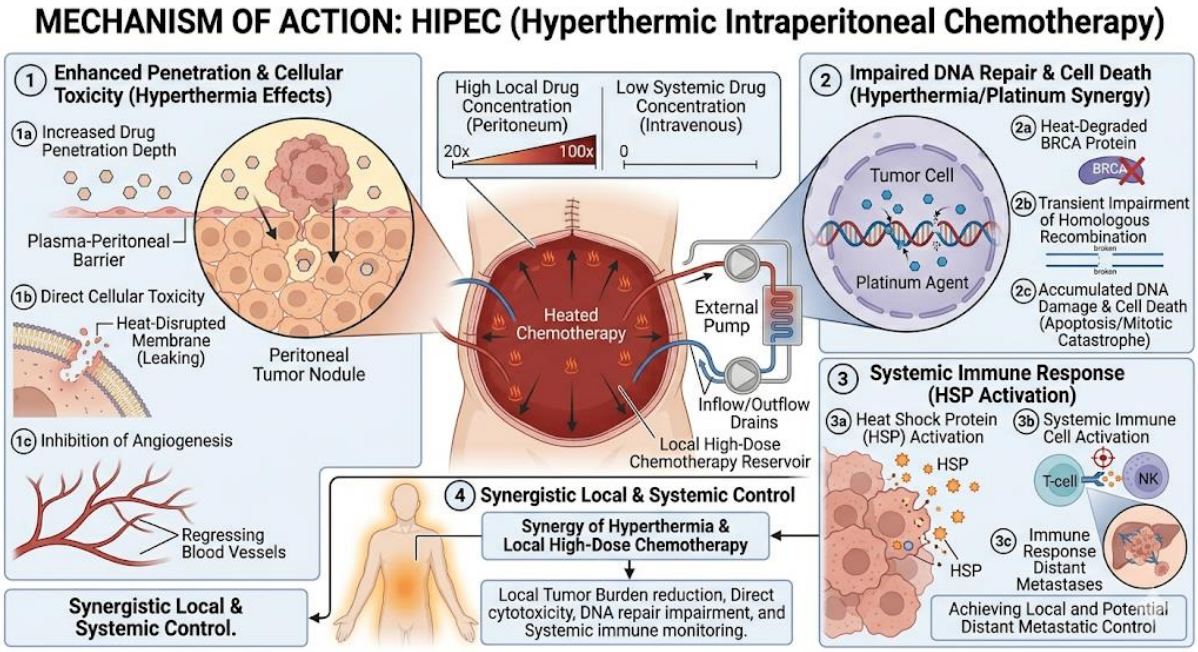

Figure 2. Mechanism of HIPEC

6. Current Role in Ovarian Cancer

6.1. Primary Ovarian Cancer and Interval Debulking Surgery (IDS)

The strongest evidence supports the use of HIPEC during IDS following NACT. The landmark OVHIPEC-1 trial (van Driel et al.) [37] demonstrated that adding HIPEC (Cisplatin 100 mg/m2 BSA) significantly improved median overall survival (OS) from 33.9 to 45.7 months and progression-free survival (PFS) from 10.7 to 14.2 months. Meta-analyses confirm this, showing a 25% reduction in the risk of death (HR 0.75) for patients with primary disease undergoing HIPEC [38]. The KOV-HIPEC-01 trial also found significant survival benefits specifically in the IDS subgroup [31].

6.2. Primary Debulking Surgery (PDS)

Conversely, there is currently no clear randomized evidence of benefit for HIPEC when administered during PDS (upfront). While some retrospective studies suggest improved OS, the subgroup analysis of the KOV-HIPEC-01 trial found no survival advantage in the PDS setting [31]. Ongoing trials like OVHIPEC-2 are expected to clarify this role [39].

Table 1. Studies Evaluating HIPEC in Primary Ovarian Cancer

Study (Year)	Clinical Setting & Stage	HIPEC Drug & Duration	Key Outcomes & Findings
Ansaloni et al. 2012 [28]	Stage III/IV (Primary subset n=9)	Cisplatin, Paclitaxel, Doxorubicin	Recurrence rate was 59%; mean recurrence time was 14.4 months.

Is KOV-HIPEC-01 trial an ongoing trial?

Diaz-Montes et al. 2018 [29]	Stage III/IV; PDS	Carboplatin (800 mg/m2 BSA), 90 min	Phase II randomized trial; results were not statistically significant in this small sample (n=19).
Lei et al. 2020 [30]	Stage III; Retrospective	Not Specified	Reported a median OS benefit of 49.8 months with HIPEC compared to 34.0 months without it.
Lim et al. 2022 (KOV-HIPEC-01) [31]	Stage III/IV; PDS or IDS	Cisplatin (75 mg/m2 BSA), 90 min	Subgroup benefit in OS and PFS for patients undergoing IDS, but no benefit observed in the PDS setting.
Antonio et al. 2022 [32]	Stage III/IV; IDS after NACT	Cisplatin (75 mg/m2 BSA), 60 min	Improved disease-free survival (DFS) (18 vs 12 months) and OS (52 vs 45 months).
Aronson et al. 2023 (OVHIPEC-1) [33]	Stage III; IDS after 3 cycles of NACT	Cisplatin (100 mg/m2 BSA), 90 min	Significant improvement in OS (45.7 vs 33.9 months) and PFS (14.2 vs 10.7 months).
Wang et al. 2024 (C-HOC) [34]	Advanced high-grade serous; IDS after NACT	Paclitaxel (75 mg/m2 BSA), 60 min	Interim analysis favored local disease control; survival data is pending.
Villarejo Campos et al. 2024 (HIPECOVA) [35]	Stage III/IV; IDS or PDS	Paclitaxel (175 mg/m2 BSA), 60 min	Improved local control; however, OS and PFS benefits were not statistically significant.
Karanikas et al. 2024 [36]	Stage III; Retrospective upfront treatment	Not Specified	Reported improved 5-year OS (69.6% vs 40.8%) in the HIPEC group.

6.3. Recurrent/Relapsed Ovarian Cancer

The role in recurrence is highly controversial. The CHIPOR trial showed a 5-year OS benefit (50% vs. 36%) in platinum-sensitive first recurrence following complete resection. However, the HORSE trial and a study by Zivanovic et al. failed to show statistically significant differences in OS or PFS. Some evidence even suggests a possible 18% increase in the risk of disease progression in the recurrent setting.

Table 2. Randomized Controlled Trials (RCTs) in Recurrent Ovarian Cancer

Study (Year)	Design	Inclusion Criteria	HIPEC Drug & Duration	Key Outcomes
Spiliotis et al. 2015 [40]	Phase 3 RCT	FIGO IIIC/IV recurrence after initial treatment	Cisplatin/Paclitaxel (platinum-sensitive) or Doxorubicin/Mitomycin (platinum-resistant), 60 min	Significant benefit: Mean survival was 26.7 vs. 13.4 months. (Note: Heavily criticized for statistical design).
Zivanovic et al. 2021 [41]	Phase 2 RCT	Platinum-sensitive recurrence	Carboplatin (800 mg/m2 BSA), 90 min	No significant difference in OS or PFS; noted a possible 18% increase in risk of disease progression.
Classe et al. 2024 (CHIPOR) [42]	Phase 3 RCT	Platinum-sensitive first relapse; complete resection (CC0/CC1)	Cisplatin (75 mg/m2 BSA), 60 min	Significant OS improvement: 5-year survival was 50% (HIPEC) vs. 36% (control).
Fagotti et al. 2025 (HORSE / MITO-18) [43]	Phase 3 RCT	Platinum-sensitive recurrence	Cisplatin (75 mg/m2 BSA), 60 min	No significant difference in OS between groups.

Table 3. Retrospective and Observational Studies in Recurrent Ovarian Cancer

Study (Year)	Design	Population Focus	HIPEC Drug(s)	Key Findings
Fagotti et al. 2012 [44]	Case-control	Platinum-sensitive recurrence	Oxaliplatin (460 mg/m2 BSA)	Secondary recurrence rate was 66.6% in HIPEC vs. 100% in control.
Bakrin et al. 2012 [45]	Retrospective Multicentric	Persistent or recurrent disease	Cisplatin with Mitomycin C or Doxorubicin	Median survival was 48 months (resistant) and 52 months (sensitive).
Le Brun et al. 2014 [46]	Retrospective Case-Control	Women with first relapse	Cisplatin, Eloxatin, Mitomycin C	The 4-year OS was 75.6% (HIPEC) vs. 19.4% (Surgery alone).

Safra et al. 2014 [47]	Case-control	Recurrent epithelial; patients with *BRCA* mutation	Cisplatin, Paclitaxel, Carboplatin, Mitomycin C	Improved median PFS (15 vs. 6 months) and 5-year survival (79% vs. 45%).
Baiocchi et al. 2015 [48]	Retrospective Observational	Platinum-sensitive secondary cytoreduction	Mitomycin C, Cisplatin, Doxorubicin	No significant difference in median OS (58.3 vs. 59.3 months).

7. Guidelines and Recommendations

Current international guidelines are cautious but recognize HIPEC as an adjunct modality with surgery.

Table 4. Guidelines and Recommendations

NCCN Guidelines [49]	Recommend HIPEC as an option for Stage III patients showing response or stable disease after NACT (specifically during IDS). The recommended agent is Cisplatin 100 mg/m2 BSA. HIPEC is not recommended for patients undergoing primary debulking.
NICE (UK) [50]	States that CRS plus HIPEC is of equivalent safety to other major abdominal procedures and provides a survival benefit, but it must be performed in specialized centers with dedicated training and clinical governance.
ESGO [51]	Recommends that HIPEC be limited to well-designed prospective randomized controlled trials.

8. Peri-operative Factors

Successful HIPEC implementation requires meticulous perioperative management. Patient selection is paramount. Ideal candidates are those with Stage III/IV disease, good performance status (ECOG 0-1), age generally under 70-75, and adequate renal function (creatinine clearance >60 ml/min). Fitness for a prolonged surgical procedure (often adding ~2 hours) must be assessed [52].

To prevent nephrotoxicity from high-dose Cisplatin, sodium thiosulphate is administered as an IV bolus (9 g/m2 BSA) followed by a 6-hour infusion [53]. Core body temperature must be monitored. Cooling blankets or ice packs may be needed to prevent systemic hyperthermia [54]. Aggressive fluid management is required to maintain a urine output of >1 ml/kg/hr. Patients should follow "Enhanced Recovery After Surgery" (ERAS) protocols. Close monitoring for acute kidney injury (AKI), electrolyte imbalances, and gastrointestinal complications (e.g., ileus or perforation) is essential [55].

9. Complications

While meta-analyses suggest that mortality rates are similar to surgery alone, HIPEC is associated with increased morbidity. The risk of grade 3-5 adverse events is significantly higher

in HIPEC cohorts [56,57]. Common events include electrolyte disturbances, anaemia, and thrombocytopenia [58]. Renal toxicity is a primary concern due to Cisplatin [59]. However, this is mitigated by sodium thiosulphate and adequate hydration. Surgical morbidities like increased rates of ileus, bowel perforation, and infection have been noted. HIPEC is associated with a significantly longer hospital length of stay [60,61].

10. Limitations

Several factors limit the widespread adoption of HIPEC. Increase in the operative time is one of them. The procedure adds an average of around two hours to already lengthy debulking surgeries [62]. There is lack of standardization and significant heterogeneity across trials regarding the optimal drug, dose, temperature, and timing. It requires specialized infrastructure and surgical expertise, making it difficult to implement in lower-resource settings. HIPEC only penetrates approximately 1-3 mm into tissue, meaning it is ineffective if macroscopic residual disease >2.5 mm remains [14-16].

11. Conclusions

HIPEC represents a significant therapeutic advance for selected patients with advanced ovarian cancer. Current evidence strongly supports its use during IDS following NACT for Stage III disease, where it offers a proven OS benefit. However, its role in the PDS and recurrent settings remains investigational. While HIPEC is associated with increased operative time and a higher risk of minor to moderate complications, it is generally considered safe when performed in specialized centers. Future research focusing on molecular biomarkers (such as *BRCA/HRD* status) and standardized protocols will be essential to refine patient selection and maximize the clinical utility of this promising treatment.

Consent for publication: There is consent for the publication of this paper.

Artificial Intelligence: During the preparation of this work, the authors used *Google NotebookLM* to summarize the available data and *Google Gemini* to generate illustrations. After using these tools, the authors reviewed and edited the content as needed and take full responsibility for the content of the published article.

COMPETING INTERESTS DISCLAIMER:

Authors have declared that they have no known competing financial interests OR non-financial interests OR personal relationships that could have appeared to influence the work reported in this paper.

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